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Statin Therapy May not Effect NLR and MPV Levels in Patients With Hypercholesterolemia: A Retrospective Study

Fatih Gungoren, MD[1], Feyzullah Besli, MD[2], Serhat Caliskan, MD[1], Ufuk Polat, MD[1], Cengiz Basar, MD[3], and Osman Akin Serdar[1]

Abstract

Statins may exert pleiotropic effects in coronary artery disease (CAD), diabetes mellitus, and familial hypercholesterolemia. We evaluated the effects of statins on the neutrophil–lymphocyte ratio (NLR) and mean platelet volume (MPV) in 261 consecutive patients with hypercholesterolemia having CAD or at high cardiovascular (CV) risk and 50 healthy participants who were retrospectively included in this study. Patients were treated with 10 to 80 mg atorvastatin or 10 to 40 mg rosuvastatin for 24 weeks according to baseline levels of cholesterol, triglycerides, and CV risk. Baseline NLR and MPV were significantly higher in patients with CAD or at high risk compared to the control group (1.89 [0.37-6.78]) vs 1.44 [0.75-2.41], $P < .001$ and 8.8 [6.27-18.6] vs 8.45 [6-11] fL, $P = .038$, respectively). The NLR, MPV, and lipid parameters were also compared in the patient group after statin treatment for 24 weeks. Lipid levels decreased but the NLR and MPV did not change significantly after the statin therapy. Further studies are needed to clarify the effect of statin therapy on NLR and MPV in patients with CAD or at high CV risk.

Keywords

statin, neutrophil–lymphocyte ratio, mean platelet volume, coronary artery disease, cardiovascular risk

Introduction

The association between serum cholesterol and cardiovascular (CV) disease is well established.[1,2] This is based on an important body of evidence, including the role of cholesterol in the inflammatory pathway and the development of atherosclerotic plaques.[3,4] In addition to their cholesterol-lowering effect, hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have favorable effects, including inhibition of platelet-dependent thrombus formation, immunomodulation, and anti-inflammatory properties.[5-7]

The inflammatory markers have been extensively studied in CV disease.[8-12] Several trials have shown a direct correlation between statin therapy and lower C-reactive protein (CRP) concentrations.[13] Moreover, several studies have demonstrated that statins lower cytokine concentrations and inhibit recruitment, migration, and cell adhesion to the endothelium by attenuating chemokine production.[13] They also inhibit inflammatory pathways regulated by proteins as Ras and Rho and increase nitric oxide production, which exerts a protective effect on the endothelium.[13] These results suggest that initiating and monitoring statin therapy on the basis of inflammatory markers, in particular CRP, neutrophil to lymphocyte ratio (NLR), and mean platelet volume (MPV), may improve CV prevention and treatment.

The NLR is a new addition to the long list of inflammatory markers.[14-18] The NLR, which is calculated from a complete blood count with differential, is an inexpensive, easy to obtain, widely available marker of inflammation. The NLR can be used in the risk stratification of patients with various CV diseases in addition to the traditionally used markers[16,17] The size of the platelets, represented by the MPV, is a potentially useful marker of platelet activity.[19,20] When platelets become activated, the MPV increases and platelets change from quiescent discs to swollen spheres with pseudopodia.[20] Large platelets are more likely to aggregate than small ones.[19,20] An elevated MPV is associated with CV and cerebrovascular disease.[21,22] Previous studies showed possible beneficial effects of statin therapy on inflammatory markers and platelet function.[23-26] However, there are limited studies about the effect of statin therapy on hematologic parameters in patients with hypercholesterolemia having coronary artery disease (CAD) or at high CV risk. Therefore, we evaluated the effects of statin treatment

[1] Department of Cardiology, Medical Faculty, Uludag University, Bursa, Turkey
[2] Department of Cardiology, Sanliurfa Mehmet Akif Inan Training and Research Hospital, Sanliurfa, Turkey
[3] Department of Cardiology, Duzce State Hospital, Duzce, Turkey

Corresponding Author:
Feyzullah Besli, Department of Cardiology, Sanliurfa Mehmet Akif Inan Training and Research Hospital, Sanliurfa, Turkey.
Email: feyzullahbesli@gmail.com

on NLR and MPV in patients with hypercholesterolemia having CAD or at high CV risk.

Materials and Methods

Study Population

A total of 261 consecutive patients with hypercholesterolemia having CAD or at high CV risk and 50 normocholesterolemic healthy participants with cardiac symptoms such as chest pain, dyspnea, and palpitations without a diagnosis CV disease served as our control group. They were admitted to the Cardiology Department at Uludag University School of Medicine Hospital, Bursa, between March 2012 and April 2014 and were retrospectively included in the study. The hypercholesterolemic group was also divided into 2 groups: taking atorvastatin (n = 146) and taking rosuvastatin (n = 115).

Risk factors and treatment goals were evaluated according to the Third Report of National Cholesterol Education Program (NCEP-III).[27] These risk factors include smoking, hypertension (blood pressure $\geq$ 140/90 mm Hg or taking antihypertensive drugs), low high-density lipoprotein cholesterol (HDL-C) <40 mg/dL, and family history of premature CAD (male or female first-degree relatives <55 or <65 years, respectively), and age (men >45 years and women >55 years). Significant CAD was defined as the presence of $\geq$1 vessel with $\geq$50% luminal diameter narrowing. All patients had at $\geq$2 coronary risk factors or CV disease. Hypercholesterolemia was defined as low-density lipoprotein cholesterol (LDL-C) > 130 mg/dL or LDL-C > 100 mg/dL, if patients had CV disease or diabetes mellitus. Patients with any of the following conditions were excluded: recent history of acute coronary syndrome (<3 months), severe valvular heart disease, pregnancy, lactation, malignancy, triglyceride concentrations >500 mg/dL, body mass index >35 kg/m^2, taking lipid-lowering drugs within 8 weeks, elevated serum creatine kinase (CK) or liver enzyme levels above the upper limit of normal, thrombocytopenia (platelet count <100 $\times$ 10^3/mm^3), thrombocytosis (platelet count >400 $\times$ 10^3/mm^3), history of hemorrhagic diathesis, acute or chronic hepatitis, chronic renal failure, hypersensitivity to statins, current use of immunosuppressive agents, hypothyroidism (thyroid-stimulating hormone >10 IU/mL), obstructive liver disease, acute renal failure, or nephrotic syndrome.

Treatment Protocol

Atorvastatin was administered at 4 alternative dosages, 10 mg (17 patients), 20 mg (64 patients), 40 mg (60 patients), and 80 mg (5 patients), and rosuvastatin was administered at 3 different dosages, 10 mg (70 patients), 20 mg (31 patients), and 40 mg (14 patients) according to baseline levels of cholesterol and triglycerides and CV risk. When the target (according to NCEP-III) level of LDL-C was not reached at 12 weeks, the dose was increased up to the end of the study at 24 weeks. At the end of the study, 7 patients were on 10 mg, 58 patients on 20 mg, 70 patients on 40 mg, and 11 patients on 80 mg of atorvastatin, while 55 patients were on 10 mg, 45 patients on 20 mg, and 15 patients on 40 mg of rosuvastatin. Before treatment, physical examination, biochemical and hematological markers, as well as electrocardiograms were recorded. At 4, 12, and 24 weeks, these procedures were repeated. The investigation conformed to the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee, and all participants gave their informed consent.

Laboratory Methods

Venous blood was obtained after a $\geq$12-hour overnight fast. Blood samples were collected in EDTA anticoagulant. Blood samples were collected from an antecubital vein by atraumatic puncture and sent to the laboratory for analysis within 2 hours after collection. Biochemical tests such as total cholesterol, LDL-C, HDL-C, triglycerides, and fasting glucose and liver enzymes such as aspartate and alanine aminotransferase (ALT) and CK were measured spectrophotometrically. The MPV, NLR, and white blood cell count were measured using a Cell-Dyne counter of Abbott Laboratories (Abbott Laboratories, Illinois). The NLR was obtained by dividing the neutrophil count by the lymphocyte count.

Safety

Adverse effects were recorded at 4, 12, and 24 weeks. Statin therapy was discontinued if the level of CK increased >5 times normal or if AST or ALT levels increased >3 times of normal at consecutive (2-week interval) visits.

Statistical Analysis

All analyses were performed using SPSS for Windows (v16.0, SPSS, Chicago, Illinois). The baseline, laboratory characteristics were presented as numbers and percentages for the categorical variables and as the means $\pm$ standard deviations (SDs) and median (range) for continuous variables. The groups were compared according to the distribution of continuous variables, with Student t or Mann-Whitney U tests. Categorical variables were compared with the chi-square test. Correlation analyses were performed with Pearson and Spearman tests. Paired t test and Wilcoxon test were used for the comparison between pre- and posttreatment levels. All tests were 2-sided and the level of significance was $P < .05$.

Results

We included 261 patients (143 males and 118 females, mean age; 62.8 $\pm$ 10.8 years) and 50 control participants (control group, 32 male and 18 female, mean ages: 61.6 $\pm$ 7.7 years). The clinical characteristics of the study population are shown in Table 1. Among patients with hypercholesterolemia, 55.6% had CAD, 36.4% had diabetes mellitus (DM), and 64.7% had hypertension (HT). Among the patients with hypercholesterolemia, family history of CAD was higher and smoking frequency tended to be higher than the control group (29.9% vs 16%, $P = .044$ and 32.6% vs 20%, $P = .077$, respectively).

Table 1. Demographic Clinical Characteristics of the Patient and Control Groups.[a]

	CAD and High Risk Group (n = 261)	Control group (n = 50)	*P* Value
Gender Male, n (%)	143 (54.8)	32 (64)	.229
Age, years	62.8 ± 10.8	61.6 ± 7.7	.184
Diabetes mellitus, n (%)	95 (36.4)	0	–
Hypertension, n (%)	169 (64.7)	0	–
Smoking, n (%)	85 (32.6)	10 (20)	**.077**
Family history of CAD, n (%)	78 (29.9)	8 (16)	**.044**
CAD, n (%)	145 (55.6)	0	–
Medications			
ACEI/ARB, n (%)	198 (75.8)	0	–
Beta-blocker, n (%)	171 (65.5)	0	
ASA, n (%)	204 (78.1)	0	
Nitrates, n (%)	92 (35.2)	0	
CaCB, n (%)	104 (39.8)	0	
Others, n (%)	64 (24.5)	0	

Abbreviations: CAD, coronary artery disease; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; CaCB, calcium channel blockers.
[a]Significant values ($P < .05$) are indicated in bold font.

Laboratory data of the patient and control groups are shown in Table 2. Patients with CAD or at high risk had significantly higher total cholesterol, triglyceride, and LDL-C levels. The NLR and MPV were also significantly higher in patients with CAD or at high risk compared to the control group (1.89 [0.37-6.78] vs 1.44 [0.75-2.41], $P < .001$ and 8.8 [6.27-18.6] vs 8.45 [6-11] fL, $P = .038$, respectively).

Changes in laboratory findings from baseline to follow-up in patients with hypercholesterolemia are shown in Table 3. Among patients with CAD or at high risk compared to baseline, statin treatment was associated with a significant decrease in total cholesterol, LDL-C, and triglyceride levels at 24 weeks. However, both NLR and MPV levels did not change significantly compared to baseline.

Adverse events. Headache, myalgia, or constipation was recorded in 6 patients on atorvastatin and 7 patients on rosuvastatin. Increase in AST and ALT activities >3 times and CK >5 times the upper limit of normal did not occur. In 2 patients from each group, AST and ALT activities increased to 2 times of upper limit of normal at week 12 of treatment with statins, and this returned to normal. Atorvastatin or rosuvastatin was not discontinued in any patients.

Table 2. Laboratory Data of the Patient and Control Groups.[a]

	CAD and High Risk Group (n = 261)	Control Group (n = 50)	*P* Value
Total cholesterol, mg/dL	233 ± 16	192 ± 11	**<.001**
Triglycerides, mg/dL	173 ± 20	130 ± 16	**<.001**
HDL cholesterol, mg/dL	44 ± 11	45 ± 14	.710
LDL cholesterol, mg/dL	155 ± 19	120 ± 13	**<.001**
GFR, mL/min	76 ± 9	75 ± 17	.731
Neutrophil count, $\times 1000/mm^3$	4.4 ± 1.3	3.6 ± 1.0	**<.001**
Lymphocyte count, $\times 1000/mm^3$	2.34 ± 0.86	2.31 ± 0.47	.764
NLR	1.89 (0.37-6.78)	1.44 (0.75-2.41)	**<.001**
Mean platelet volume, fL	8.8 (6.3-18.6)	8.4 (6-11)	**.038**

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; GFR, glomerular filtration rate; NLR, neutrophil–lymphocyte ratio.
[a]Significant values ($P < .05$) are indicated in bold font.

Table 3. Effect of Statin Therapy on Laboratory Data in Patients With Hypercholesterolemia.[a]

	Baseline, n = 261	After Treatment, n = 261	*P* Value
	233 ± 16	188 ± 19	**<.001**
Triglycerides, mg/dL	173 ± 20	144 ± 11	**<.001**
HDL cholesterol, mg/dL	44 ± 11	42 ± 9	.118
LDL cholesterol, mg/dL	155 ± 19	117 ± 13	**<.001**
GFR, mL/min	76 ± 9	75 ± 8	.416
AST, U/L	20 ± 7	22 ± 8	**<.001**
ALT, U/L	20 ± 11	23 ± 13	**<.001**
CK, U/L	74 ± 10	95 ± 15	**<.001**
Neutrophil, $\times 1000/mm^3$	4.40 ± 1.3	4.61 ± 1.5	**.002**
Lymphocyte, $\times 1000/mm^3$	2.34 ± 0.86	2.40 ± 0.80	.162
NLR	1.89 (0.37-6.78)	1.9 (0.62-8)	.962
Mean platelet volume, fL	8.8 (6.3-18.6)	8.7(6.3-17.3)	.107

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; GFR, glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatine kinase; NLR, neutrophil–lymphocyte ratio.
[a]Significant values ($P < .05$) are indicated with bold font.

Discussion

In the present study, statin therapy significantly improved the lipid profile but did not change MPV or NLR in patients with hypercholesterolemia having CAD or at high CV risk at 24 weeks.

Statins have beneficial effects on morbidity and mortality in patients with CAD.[28] There is increasing evidence that statins exert anti-inflammatory and antithrombotic effects.[29] Platelets play a crucial role in the pathophysiology of CAD.[30] Large platelets are more active and have higher thrombotic potential.[31] Increased platelet activity is associated with atherosclerotic disease. Increased platelet size has been reported in patients with vascular risk factors such as DM or hypercholesterolemia.[32,33] There is evidence that high LDL-C levels could trigger spontaneous platelet aggregation.[32,33] In this context, it was also reported that the MPV significantly decreased after rosuvastatin treatment in patients with primary hypercholesterolemia.[34]

Statins have anti-inflammatory effects. Several studies have reported reductions in inflammatory markers after statin use.[35,36] It was demonstrated in a prospective, randomized, double-blind, crossover trial of patients with hyperlipidemia that the decrease in CRP levels by statins was a class effect.[37]

It was recently reported that hypercholesterolemia was associated with increased NLR and MPV.[38] Similarly, we also found that NLR and MPV were higher in patients with hypercholesterolemia having CAD or at high CV. The elevated NLR and MPV may be associated with increased platelet activity and accelerated inflammatory process in our study population. Akin et al showed that atorvastatin significantly decreased the NLR and MPV in patients with primary hypercholesterolemia.[38] However, Akin et al did not assess the presence of CAD, and the patients in their study received atorvastatin as primary prevention.[38] In another study, atorvastatin significantly improved lipid parameters but did not significantly change the level of hematological or coagulation parameters.[39] Similarly, we found that statin therapy significantly decreased total cholesterol, LDL-C, and triglycerides levels but did not reduce NLR or MPV in our study population.

The reason for this result may be due to the following: First, our study sample had a high-risk profile ($\geq$ 2 coronary risk factors or CAD). Second, the patients did not only have hypercholesterolemia but also a substantial frequency of CAD, DM, hypertension, smoking, or family history of premature CAD. Third, patients were on different drug treatments for CAD, DM, or HT. However, since all the patients continued to receive their baseline medication during the follow-up period, we assume that other drugs did not affect our results.

This study has several limitations. First, it was performed retrospectively from a hospital archive system. Second, patients were followed only for 24 weeks, and clinical outcomes were not evaluated. Another limitation is that the study period was approximately 2 years, and MPV and NLR may be affected by various factors including changes in CAD or regulation of DM and HT, new diseases, and drugs during this time. Furthermore, CRP or another inflammation marker was not evaluated.

Neutrophil–lymphocyte ratio and MPV, an inflammatory biomarker, can be of predictive and prognostic value for CV events.[15,17,18,21] However, the effect of statin therapy on NLR and MPV is not clear in hypercholesterolemia with CAD or at high CV risk. Further studies are needed to clarify the clinical significance of statin therapy on hematological parameters and the association with clinical outcomes.

Authors' Note

All the authors contributed to the article with (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content and have read and approved submission of the manuscript. The final manuscript has been approved by all authors and the authors have taken due care to ensure the integrity of the work.

Declaration of Conflicting Interests

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